that level of change in a given outcome parameter that would be deemed of clinical importance. We wholeheartedly agree that consensus in this regard would be highly desirable and are aware, for example, of the recommendation, by one regulatory body, that a 10% improvement in a cardinal symptom, such as pain, be the threshold for approval of a new compound. We would contend, however, that this approach may be overly simplistic and would stress the unique challenges posed by studies performed in a heterogeneous population, such as IBS, where a response, deemed modest for an entire group, may be much more impressive in a subgroup within this population. Unfortunately, our ability to dissect the IBS patient population on the basis of pathophysiology and, thereby, therapeutic responsiveness, remains primitive. With regard to our study,[1] we would emphasize that the therapeutic gain observed was, at the very least, in the range of that reported for some recently approved compounds.[2–4] We would concede that our sample size did not permit a delineation of responders. The latter should, clearly be an important goal of future studies.

Our own experience, in a further study of *Bifidbacterium infantis* 35624 in IBS, also cautions against an over-reliance on a single symptom as a primary outcome measure.[5] IBS sufferers experience different symptoms which are highly variable in terms of both severity and impact on quality of life. The "big picture" for an individual IBS subject may be captured more accurately and in a more clinically meaningful manner by some form of global assessment; in data presented at the recent DDW we observed a far greater improvement in a global assessment instrument than in any individual cardinal symptom.[5] Pending the development of a reliable biomarker for IBS, consensus must be reached on the critical issue of the optimal outcome measure(s).

Dr van Zanten also points, correctly, to the nature of the patients we studied. We readily acknowledge that they were at the "mild" end of the IBS spectrum. Indeed, we deliberately set out to reflect IBS in the community, rather than at a referral centre; thus the ranges of symptom severity reported. We would contend that our ability to demonstrate a significant therapeutic gain, in the context of low baseline scores, is a strength and not a weakness of the study. Clearly, we look forward to future studies of our *Bifidobacterium infantis* 35624, across the IBS spectrum.

The field needs more studies of therapeutic interventions in IBS; such studies should simultaneously and rigorously assess the "real" clinical validity and reproducibility of our outcome measures.

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Prostate Radiotherapy Is Associated With Second Cancers in Many Organs, not Just the Colorectum

Dear Sir:

The recent study by Baxter et al[1] on rectal cancer associated with prostate cancer radiotherapy extended by several years the follow-up period from our earlier study,[2] based on the same SEER cancer registry database. The more extended follow-up confirms our earlier conclusion that rectal cancer is significantly elevated in long-term survivors of prostate cancer radiotherapy, compared with a comparison group of prostate cancer patients who underwent surgery alone. Baxter et al[1] report risks for radiation-associated rectal cancer that are very similar to our earlier estimates; specifically, they estimate a hazard ratio (radiotherapy vs. surgery) of 1.7 (95% confidence intervals: 1.4, 2.7) for cancers diagnosed more than 5 years after treatment, which may be compared with our earlier estimates[2] of 1.3 (95% CI: 0, 1.8) for rectal cancers diagnosed more than 5 years after treatment, and 2.1 (95% CI: 0.1, 2.9) for rectal cancers diagnosed more than 10 years after treatment.

However, while the recent study by Baxter et al[1] focuses only on radiation-associated colorectal cancers, it is important to note that other cancers are also likely be related to the radiotherapy. For prostate radiotherapy patients, Figure 1[2] shows the breakdown of the

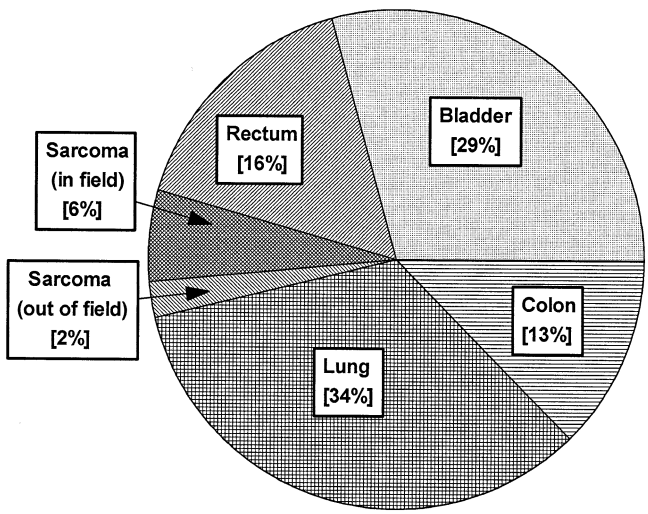

Figure 1. Estimated percentage contributions to the total numbers of radiation-associated solid cancers that were diagnosed 10 or more years after prostate cancer radiotherapy.[2] Only those cancers that showed a statistically significant increase for radiotherapy vs. surgical treatment of the primary prostate cancer were included. Based on data reported to the SEER data base, for patients diagnosed with primary prostate cancer between 1973 and 1993.

total number of radiation-associated cancers diagnosed 10 or more years after prostate radiotherapy (only cancers with statistically significant increases are shown). It can be seen that, though colorectal cancers are important, they constitute less than one third of the overall radiation-associated cancer risk, the sites at highest risk being bladder and lung.

Figure 1 indicates that radiation-associated cancers can occur not only in organs proximal to the prostate, such as the rectum[1,2] and the bladder,[2,3] but also in organs quite distal to the prostate. For example, while the lung is considerably distal to the prostate, it still receives significant radiation exposure during prostate radiotherapy, due to scattered radiation, as well as leakage from the radiation source.[4,5] Indeed, because of radiation scatter and leakage, there in fact are no organs in the body that are "non-irradiated sites," to use Baxter's terminology. Thus, for example, while the lung does receive a considerably lower radiation dose during prostate radiotherapy than do the GI or GU organs, the risks for radiation-induced lung cancer after prostate radiotherapy are significant, as they are after cervical radiotherapy.[6] Thus one cannot, as Baxter et al[1] imply, exclude the possibility of significant radiation-associated cancer risks in sites distal to the prostate, which received low or moderate radiation doses during treatment.

In summary, while the analysis by Baxter et al[1] adds several more years of follow-up to earlier SEER analyses[2,3] of second cancers associated with prostate radiotherapy, by focusing only on induced colorectal cancers, the paper presents only a partial picture of potential radiotherapy-related cancers. In the context of radiation-induced second cancers, we need to be concerned not only about organs proximal to the primary treated tumor, but also about radiogenic organs throughout the body.

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Reply. We would like to thank Brenner et al[1] for their comments supporting the findings of our study. While we agree that a radiation dose is given to tissues outside of the high-dose radiation volumesduring radiation therapy for cancer, most studies have demonstrated that the major carcinogenic effect from radiation is within the high-dose region.[1,2] We certainly agree that organs other than the rectum are exposed to a high does of radiation during radiation therapy for prostate cancer, particularly the bladder, and this must be considered for surveillance after prostate irradiation. The increased risk of lung cancer in patients who undergo irradiation for prostate cancer lung is an intriguing finding. Although the lung receives a radiation dose (combination of scatter and leakage) of approximately 60 cGy during prostate cancer treatment, this dose does not produce a major increase in cancer formation in most organs; other exposures, such as cigarette smoking, may act synergistically with irradiation to increase lung cancer incidence (as has been shown in radium miners).[3] However, important risk factors for lung cancer, particularly cigarette smoking, may not be equally distributed between those treated with radiation therapy and those treated with surgery, and this may result in an apparent increased risk of lung cancer in the irradiated group due to confounding.

Our study[4] and Brenner's study[1] employed cohort designs and therefore confounding due to selection bias is a concern and may account for apparent differences in rectal cancer rates between those who undergo surgery and those who undergo irradiation. For example, in our study, we found that patients undergoing irradiation were significantly older than those undergoing surgery. As increasing age is a known risk factor for rectal cancer, patients undergoing irradiation in both studies were at a higher baseline risk of rectal cancer than patients who had surgery only. Although we controlled for age in our analysis, we could not control for unmeasured confounders, and thus the potential for selection bias remained. By demonstrating a significant increase in cancer in the area in the high-dose region (the rectum) but no significant increase in areas outside the high-dose region (the remainder of the colon), we were able to conclude that irradiation has a direct effect on rectal carcinogenesis, and this effect cannot be explained by any baseline higher risk of colorectal cancer in those undergoing radiation therapy. Our consideration of the potential influence of selection bias represents a major improvement over the methods of previous research in this area[1,5,6] and greatly strengthens our conclusions.

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